



THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

SCHOENFELD ET AL

Serial No.: 09/806,400

Filed: March 30, 2001

For: A COMPOSITION FOR THE  
PREVENTION AND/OR  
TREATMENT OF  
ATHEROSCLEROSIS

Examiner: SCHWADRON, Dr. RONALD B.

Group Art Unit: 1644

Attorney  
Docket: 01/21885

Commissioner of Patents and Trademarks  
Washington, D.C. 20231

**DECLARATION OF PROF. DROR HARATS UNDER 37 CFR 1.132**

I am presently employed as the head of the "Institute of Lipids and Atherosclerosis" at the "Sheba" Medical Center in Tel-Hashomer, Israel. I am an associate professor of Medicine at the "Sackler" School of Medicine, Tel-Aviv University, Tel-Aviv, Israel. I also serve as the Secretary of the Israeli Society for Research, Prevention and Treatment of Atherosclerosis, and drafted the Guidelines for Prevention of Cardiovascular Diseases in Israel, and am a member in good standing of the European Taskforce for Prevention and Treatment of Atherosclerosis and Cardiovascular Diseases. I received my M. D. degree from the Hebrew University Hadassah Medical School, Jerusalem, Israel, and during 1991-1994 worked as a post-doctoral fellow at the UCSF, USA.

My research focuses on atherosclerosis. Since the beginning of my career, I have published over 80 scientific articles in highly regarded journals and books, and have presented my achievements at many international

scientific conferences.

I am also a member of The International Society for Atherosclerosis and The European Atherosclerosis Society and the American Heart Association, and was recognized in 1995 a "Young Leading Investigator" both by the International Society of "Drug Affecting Lipid Metabolism" and the "Yoshida Heart Institute" in Japan. I have also served as consultant, collaborator and board member for numerous pharmaceutical and biotechnology companies in Israel, the USA and Europe.

I am a co-inventor of the subject matter described and claimed in the above-referenced U.S. Patent Application.

I have read the Official Actions issued with respect to the above-identified application.

The Examiner has stated that the present invention of a composition for an immunological oral-tolerance inducing composition for the prevention and/or treatment of atherosclerosis is anticipated by, and would have been obvious to one of ordinary skill in the art in view of the referenced prior art. I am of the opinion that the prior art does not anticipate, nor provides motivation for one of ordinary skill in the art to combine the teachings of Strober et al. with Hansson et al., Resch et al. and Sima, et al., and that the scope and content of the prior art, which discloses a method for enhancement of oral tolerance to autoimmune diseases (Strober et al.) and the presence of anti-oxidized LDL antibodies in atherosclerosis (Hansson et al., Resch et al. and Sima et al.) are greatly distinguished from and dissimilar to the present invention.

The present invention is of a unique oral-tolerance inducing composition which is not only novel and nonobvious, but provides an unexpected and previously unavailable basis for prevention and/or treatment of atherosclerosis, and as such responds to a long-felt need in the field of cardiology and preventive medicine.

Strober et al. teaches enhancing oral tolerance to an antigen by suppressing the proinflammatory cytokine IL-12, specifically for the treatment of autoimmune disease. As discussed in detail in the accompanying response to Official Action, atherosclerosis is primarily a disease of deranged lipid metabolism, which does not exhibit the hallmark flare and remission of autoimmune disease, does not respond to conventional immune suppression, and is therefore not commonly classified as an autoimmune disease. Thus, although Hansson et al., Resch et al. and Sima, et al. do teach the presence of anti-oxidized LDL antibodies in atherosclerosis, the significance of Ox LDL to the pathogenesis of atherosclerosis, at the time the invention was made, remained unclear and controversial. For example, in contrast to classic response to autoantigens, it was well known in the art that OxLDL can induce atherosclerosis, while anti-OxLDL antibodies conferred partial protection. Further confounding understanding of the role of OxLDL and potential therapeutic applications is the often-repeated fact of regular dietary intake of significant amounts of OxLDL in cooked animal products.

Applicant has submitted a series of drawings, illustrating the possible effects of oral administration of an antigen on progression of atherosclerosis. As detailed in the accompanying response, and hereinabove, the illustrations depict the inability to infer, without extensive experimentation, which formulations, doses or regimen of treatment will result in induction of oral tolerance (hyporesponsiveness, Panel I, and Oral Tolerance, Panel II), and, on the other hand, which will further stimulate inflammatory response of the gut associated lymph tissue (GALT) (hyperresponsiveness, Panel II), exacerbating disease. One example of such inflammatory immune response to oral feeding of a well known autoantigen is described in Blanas E, et al. (Science 1996;274:1710, enclosed herewith).

Among the criteria applied to determine non-obviousness of an invention is demonstration of unexpected results. While reducing the present invention to practice, employing the methodology disclosed in the instant

specification, we have unexpectedly uncovered further aspects of the prevention and/or treatment of atherosclerosis by oral feeding with Ox LDL, strengthening this unique and novel approach to the disease.

Specifically, in one experiment a dose-dependent reduction in atherosclerotic lesions in genetically susceptible (LDL-RD and Apo-E “knock out”) mice was observed following oral administration of Ox LDL according to the methods of the present invention, thus further confirming the range of “therapeutically effective amount” disclosed in the instant specification. Within the range of 10-1000 µg per mouse, the strongest effect on atherogenesis (45 % reduction in lesions) was observed at a dose of 100 µg/mouse. In another important series of experiments, a significant, dose-dependent reduction of T-cell proliferation in lymph nodes of LDL-RD and Apo-E “knock out” mice following oral administration of Ox LDL according to the methods of the present invention was observed. Whereas oral administration of as little as 10 µg/mouse Ox LDL produced a 49 % inhibition of proliferation of Ox LDL-responsive lymphocytes, indicating the ability of orally administered Ox LDL to induce tolerance by clonal anergy/deletion of specific lymphocyte populations. In yet a further series of experiments, immune tissue-specific suppression of the pro-inflammatory cytokine INF $\gamma$ , and induction of the anti-inflammatory, Th-2 specific cytokine IL-10 were observed in LDL-RD and Apo-E “knock out” mice following oral administration of Ox LDL according to the methods of the present invention. Such a demonstration of immune modulation by oral administration of Ox LDL now provides the basis for determining therapeutically effective compositions and doses of Ox LDL of the present invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment, or both, under Section 1001 of Title 18 of the United states Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

November 21, 2002



Prof. Dror Harats

*Enc.:*

CV of Prof. Dror Harats

Drawings illustrating GALT Immune Response: Panel I and Panel II

Copy of Blanas, E et al. Science 1996;274:1710.

**CURRICULUM VITAE**

**Name:** Dror Harats M.D.      **Identity No.:** 5449664-1  
**Place of work:** The Sheba Medical Center  
Tel Hashomer, 52621      **Phone No.:** (03)5302940  
**Faculty/Hospital:** The Sheba Medical Center  
Tel Hashomer, 52621      **Department:** The Institute  
of Lipid and Atherosclerosis  
Research.  
**Home Address:** 71 Mendes St., Ramat-Gan      **Phone No.:** (03)5357650  
**Date & Place of Birth:** 17/7/56      Israel  
**ZAHAL Military Service:** Enlisted: February, 1982.  
Discharged: February, 1985.  
**Marital Status:** married      **No. of Children:** 2

**A. EDUCATION**

<b>Period of Study</b>	<b>Name of University</b>	<b>Subject</b>	<b>Degree</b>	<b>Date</b>
1974-1981	Hebrew University-Hadassah Medical School, Jerusalem, Israel.	Medicine	M.D.	1982

**Specialization Certificate:** Internal Medicine: (1989)  
Pulmonary Medicine: (1995)

**M.D., Thesis:** Non-Invasive Evaluation of Complete Left  
Bundle Branch Block, 1982.

**Name of Supervisor:** Prof. Alexander Batler, Sackler Faculty of  
Medicine, Tel Aviv University.

**B. FURTHER STUDIES**

<u>Period of Study</u>	<u>Name of University</u>	<u>Subject &amp; Degree</u>	<u>Date</u>
1985-1989	Hebrew University-Hadassah Medical School, Jerusalem, Israel.	Specialization in internal Medicine.	1989
1991-1994	The University of California San Francisco San Francisco, USA.	Specialization in Pulmonary & Critical Care Medicine.	1994
1992-1994	The University of California San Francisco San Francisco, USA.	Postdoctorate Molecular Genetics.	1994

**C. ACADEMIC EXPERIENCE**

<u>Period</u>	<u>Name of Institution</u>	<u>Department</u>	<u>Rank/Function</u>
2001-	Sheba Medical Center Tel-Hashomer, Israel.	Basic Research Committee	member of the committee
1999-	Sackler School of Med., Tel Aviv University, Israel	Internal Medicine	Associate Professor
1998-	Sheba Medical Center Tel-Hashomer, Israel.	Helsinki- IRB Committee	Head of the committee
1996-	Sheba Medical Center Tel-Hashomer, Israel.	Institute of Lipid and Atherosclerosis Research.	Head of the Institute
1995-1999	Sackler School of Med., Tel Aviv University, Israel	Internal Medicine	Senior lecturer
1994-1996	Sheba Medical Center Tel-Hashomer, Israel.	Institute of Lipid And Atherosclerosis Research.	Senior Scientist & Physician.
1992-1994	Syntex Discovery Research Palo-Alto, California, USA.	Molecular Genetics.	Visiting Scientist
1991-1994	The University of Ca. San Francisco, USA.	Cardiovascular Research Institute.	Postdoctorate
1990-1995	Hebrew University Hadassah Medical School, Jerusalem, Israel.	Internal Medicine	Lecturer
1987-1990	Hebrew University Hadassah Medical School, Jerusalem, Israel.	Internal Medicine	Instructor

**D. CLINICAL EXPERIENCE**

<b><u>Period</u></b>	<b><u>Name of Institution</u></b>	<b><u>Department</u></b>	<b><u>Rank/Function</u></b>
1996-	Sheba Medical Center Tel-Hashomer, Israel.	Institute of Lipid And Atherosclerosis Research.	Head of the Institute
1994-1996	Sheba Medical Center Tel-Hashomer, Israel.	Institute of Lipid And Atherosclerosis Research.	Attending Physician
1994-	Sheba Medical Center Tel-Hashomer, Israel.	Institute of Pulmonary Medicine.	Attending Physician
1991-1994	The University of California San Francisco San Francisco, USA.	Pulmonary & Critical Care Medicine	Fellow
1989-1991	Hebrew University Hadassah Medical School, Jerusalem, Israel.	Internal Medicine	Attending Physician
1987-1991	Ministry of Defense.	Rehabilitation	District Physician.
1985-1989	Hebrew University Hadassah Medical School, Jerusalem, Israel.	Internal Medicine	Resident
1982-1985	ZAHAL	The Medical Forces	Captain
1981-1982	Sheba Medical Center Tel Hashomer, Israel.	Rotating Internship	Intern

<b><u>Boards &amp; Licenses</u></b>	VQE-ECFMG, 1981. ECFMG #328-876-8, 1981. Israel, Medical License #017264, 1984. Israel-Boards of Internal Medicine, part 1 & 2, with distinction, 1988 & 1989. Internal Medicine #10791, 1989. FLEX #000088768 part 1 and 2, 1993. Nebraska, license to practice medicine #19509, 1994. Israel-Board in Pulmonary Medicine, part 1& 2, 1995.
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**E. ACADEMIC & PROFESSIONAL AWARDS****Prizes**

1975	Hebrew University-Hadassah Medical School	“Excellency in Anatomy”	\$2,000
1975-1980	Hebrew University-Hadassah Medical School	“Excellence in Studies”. (Each year)	\$3,000
1988	Hebrew University-Hadassah Medical School	<b>Faculty-Prize for Research</b> “Preferential metabolism by (Sole and Goldberg prize): macrophages of conditioned rabbit hypercholesterolemic remnant lipoproteins.”	\$3,000
1989		<b>Award for Outstanding lecturer.</b>	
1990	Hebrew University-Hadassah Medical School (Dr. M. Sherwood prize):	<b>Faculty-Prize for Research</b> “Cigarette smoking render LDL susceptible to peroxidative modification and enhanced metabolism by macrophages.”	\$4,000
1995	Giovanni Lorenzini Medical Foundation	<b>Young Investigator Award,</b> Targeting gene expression to the vascular wall in transgenic mice using the murine preproendothelin-1 promoter	\$2,000
1995	Sheba Medical Center Tel-Hashomer, Israel.	“El-Zohar” Research Prize	\$4,000

**E. ACADEMIC & PROFESSIONAL AWARDS (cont.)****Prizes**

1996	Uchida International Award Japan Foundation of Cardiovascular Research	<b>Young Investigator Award,</b> Targeting gene expression to the vascular wall in transgenic mice using the murine preproendothelin-1 promoter	¥1,000,000
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**Fellowships**

1979	Albert Einstein College of Medicine New York, NY, USA.	Fellowship Prize.	\$3,500
1991	Israel Medical Association.	Fellowship-Prize.	\$4,000
1992	The University of California San Francisco San Francisco, USA.	"Boehringer Ingelheim" Honorary Fellowship	\$25,000

**Grants**

1991	The Israel Academy of Sciences and Humanity	"Wolfson" grant	\$20,000
1992-1994	NIH	Fogarty International Fellowship Grant.	\$70,000
1995-1998	United State-Israel Binational Science Foundation.	Binational Grant "Overexpression of 15LO in Transgenic Mice".	\$110,000
1995	Syntex Discovery Research Palo-Alto, California, USA.	Research Grant in Vascular Biology	\$10,000
1995-1998	The Ministry of Science and The Arts	Tissue Specific Gene Therapy to Neovascular Endothelial Cells	\$40,000
1996-1997	Israel Cancer Association	Tissue Specific Gene Therapy to Neovascular Tumoral Cells	\$25,000

**E. ACADEMIC & PROFESSIONAL AWARDS (cont.)****Grants**

1996-2000	Mercator Genetics	The "Asthma-Gene" in the Jewish population in Israel	\$507,000
1997-1998	Tiber	"Overexpression of 15LO in Transgenic Mice".	\$3000
1998-2000	Recanati Medical Foundation	Long QT Syndrome: The molecular basis of a new mutation.	\$22,000
1998-1999	MSD Foundation Research Grant	Secondary Prevention Study ("HOLEM")	\$480,000
1998-1999	Gotvirt Diabetes Research Fund	Israel cohort of Glucose intolerance (Phase 3)	\$5,000
1999	Ministry of Health, Chief Scientists office, Jerusalem	Oral Tolerance in Atherosclerosis	₪20,000
2000-2001	Recanati Medical Foundation	Tissue Specific Gene Therapy to Neovascular Tumoral Cells.	\$25,000
2000-2001	Israel Cancer Association	Using Preproendothelin promoter to direct pro-apoptotic genes to endothelial cells in tumor angiogenesis.	₪65,000
1999-2002	BMS Genetic Research Grant	Genetics of COPD	\$320,000
2000-2003	Cardimmune	Immunomodulation and oral tolerance in atherosclerosis.	\$240,000
2001-2002	Olivia	The effect of fatty acids composition on atherogenesis.	\$150,000
2001-	Serono	Soluble LDL Receptor	\$96,000

**E. ACADEMIC & PROFESSIONAL AWARDS (cont.)****Grants**

2002-	Nikken-Shohonsha	9-cis retinoic Acid-Lipid Metabolism & Atherogenesis.	\$305,000
2000-2002	Roche	Xenical in severe hypertriglyceridemic patients.	CHF 131,200
2001-2002	קרן תזבונות	Using Preproendothelin promoter to direct pro-apoptotic genes to endothelial cells in tumor angiogenesis.	₪ 150,000

**Academic Awards**

1999-	Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel	Associate Professor in Internal Medicine
1995-1999	Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel	Senior lecturer in Internal Medicine
1990-1995	Hebrew University Hadassah Medical School, Jerusalem, Israel.	Lecturer in Internal Medicine
1987-1990	Hebrew University Hadassah Medical School, Jerusalem, Israel.	Instructor in Internal Medicine

**F. MEMBERSHIP IN PROFESSIONAL SOCIETIES**

<u>Since</u>	<u>Society</u>	<u>Country</u>
1981	Israel Medical Association.	Israel
1987	Israel Society for Research, prevention and Treatment of Atherosclerosis	
1989	International Atherosclerosis Society.	USA
1991	American Lung Association.	USA
1991	American Thoracic Society.	USA
1991	American Clinical of Chest Physicians.	USA
1992	American Heart Association.	USA
1994	Israel Society of Pulmonary Medicine.	Israel
1996	European Atherosclerosis Society	
1996	International Task Force for prevention and Treatment of Atherosclerosis	
1998	Israel Heart Society	Israel
1998	Israel Task Force for prevention and Treatment of Atherosclerosis	Israel
2000	Israel Society of Obesity	Israel

## **G. ACTIVE PARTICIPATION IN SCIENTIFIC MEETINGS**

<b><u>Year</u></b>	<b><u>Name of Meeting</u></b>	<b><u>Location</u></b>
<b>2002</b>	Irish Angiology Symposium- <b>Invited speaker</b>	Belfast, Ireland
<b>2002</b>	International Symposium on Infection & Atherosclerosis <b>Invited speaker</b>	Washington DC, USA
<b>2002</b>	6 <sup>th</sup> International Dead sea symposium – <b>Invited speaker</b>	Tel-Aviv, Israel
<b>2001</b>	37 <sup>th</sup> EASD Annual Meeting – <b>Invited speaker</b>	Glasgow, Scotland
<b>2001</b>	International Diabetes and Atherosclerosis Symposium – <b>Invited speaker</b>	Troon, Scotland
<b>2001</b>	Orphan Nuclear Receptors	Sunnyvale, CA., USA
<b>2001</b>	American Diabetes Association – <b>Invited speaker</b>	Tempe, Arizona, USA
<b>2001</b>	EAS workshop on the Immune System & atherosclerosis - <b>Chairman</b>	Geneva, Switzerland
<b>2001</b>	The 7 <sup>th</sup> Annual meeting of the Society for Research, Prevention and Treatment of Atherosclerosis	Eilat, Israel
<b>2000</b>	XIIth International Symposium on Atherosclerosis – <b>Invited speaker</b>	Stockholm, Sweden
<b>2000</b>	3 <sup>rd</sup> Annual Meeting of American Society of Gene Therapy	Colorado, USA
<b>2000</b>	2000 EAS workshop, Low HDL in Cardiovascular diseases	Istanbul, Turkey
<b>1999</b>	1999 NAASO Annual Meeting	Charleston, SC, USA
<b>1999</b>	Immunological Aspects on Cardiovascular Diseases – <b>Invited speaker</b>	Stockholm, Sweden
<b>1999</b>	46 <sup>th</sup> annual meeting of the Israel Heart Society	Tel-Aviv, Israel
<b>1999</b>	Gordon Researc Conferences, Atherosclerosis	Boston, USA
<b>1999</b>	5 <sup>th</sup> Int. Symposium: Multiple risk factors in cardiovascular disease – <b>Invited speaker</b>	Venice, Italy
<b>1999</b>	2 <sup>nd</sup> International Congress of Autoimmunity <b>Invited speaker</b>	Tel Aviv, Israel
<b>1999</b>	71 <sup>th</sup> European Atherosclerosis society – <b>Invited speaker</b>	Athens, Greece
<b>1999</b>	71 <sup>th</sup> Scientific Sessions, American Heart Assoc.	Dallas, USA
<b>1998</b>	The Scientific Meeting of the Society for Research, Prevention & Treatment of Atherosclerosis.	Ashkelon, Israel
<b>1998</b>	70 <sup>th</sup> European Atherosclerosis society – <b>Invited speaker</b>	Geneva, Switzerland
<b>1998</b>	European Heart Society.	Vienna, Austria
<b>1998</b>	The Annual Meeting of the Society for Research, Prevention & Treatment of Atherosclerosis.	Eilat, Israel
<b>1998</b>	Keystone Symposia on Gene Therapy	Keystone, USA
<b>1997</b>	The 11th International Atherosclerosis Society – <b>Invited speaker</b>	Paris, France
<b>1997</b>	70 <sup>th</sup> Scientific Sessions, American Heart Assoc.	Orlando, USA
<b>1997</b>	American Thoracic Society International conf.	SF, USA
<b>1997</b>	Keystone Symposia on Atherosclerosis	Keystone, USA

**G. ACTIVE PARTICIPATION IN SCIENTIFIC MEETINGS (cont.)**

<u>Year</u>	<u>Name of Meeting</u>	<u>Location</u>
1996	International Task Force for prevention and Treatment of Atherosclerosis – <b>Invited speaker</b>	Berlin, Germany
1996	The Israel Society for Arteriosclerosis Research.	Jerusalem, Israel
1996	64th European Atherosclerosis society.	Florence, Italy
1996	The Annual Meeting of the Society for Research, Prevention & Treatment of Atherosclerosis.	Eilat, Israel
1995	The Israel Society of Pulmonary Medicine	Tel Aviv, Israel
1995	The Israel Society for Arteriosclerosis Research.	Tel-Aviv, Israel
1995	68th Scientific Sessio, American Heart Assoc.	Anahime, USA
1995	9th Inter. Symp; Drug Affecting Lipid Metabolism.	Huston, USA
1995	68th Scientific Sessions, American Heart Assoc.	Anaheim, USA
1995	64th European Atherosclerosis society – <b>Invited speaker</b>	Utrecht, Netherlands
1995	American Thoracic Society International conf.	Seattle, USA
1995	5th Rappaport Symposium on Modified Lipo-proteins & Antioxidant in Atherosclerosis.	Shavei-Zion, Israel
1995	FASEB Conference, Experimental Biology – <b>Invited speaker</b>	Atlanta, USA
1995	The Annual Meeting of the Society for Research, Prevention & Treatment of Atherosclerosis.	Eilat, Israel
1994	67th Scientific Sessions, American Heart Assoc.	Dallas, USA
1994	the 9th International Conference on Prostaglandins & Related Compounds.	Florence, Italy
1994	American Thoracic Society International conf.	Boston, USA
1994	The 5th UCSF Pulmonary Research Meeting.	Asilomar Ca., USA
1993	66th Scientific Sessions, American Heart Assoc.	Atlanta, USA
1993	American Thoracic Society International conf.	San Francisco, USA
1993	The 4th UCSF Pulmonary Research Meeting.	Asilomar Ca., USA
1993	The Annual AIDS Scientific Meeting.	San Francisco, USA
1992	American Thoracic Society International conf.	Orlando, USA
1991	The 9th international symposium on atherosclerosis.	Chicago, USA
1990	The Israel Society for Arteriosclerosis Research.	Tel-Aviv, Israel
1990	55th European Atherosclerosis Society.	Brugge, Germany

**STUDENTS SUPERVISED BY CANDIDATE****G.1 M.D. STUDENTS****The Hebrew University Hadassah Medical School Jerusalem.**

1990-1991      Peleg Ben Galim      M.D.  
**Thesis:**      "Lipid peroxides in down's syndrome: A study related to the paucity of atherosclerosis in this condition".

**Sackler School of Medicine Tel Aviv University**

1998            Yoav Keidar          M.D. Thesis  
**Thesis:**       "Effect of Colchicine on Atherosclerosis in LDL-Receptor deficient mice".

1998            Yaniv Sherer          M.D. Thesis  
**Thesis:**       "Magnesium fortification of drinking water and atherosclerosis in LDL-receptor ko mice."

2001            Ayana Dvir          M.D. Thesis  
**Thesis:**       "The effect of Omapatrilat on atherogenesis in a combined atherosclerosis – diabetes mouse model in LDL receptor deficient streptozotocin treated mice".

**G.2 M.Sc. & Ph.D. STUDENTS**

1995-2001      Nira Blum            Ph.D.  
**Thesis:**       "Tissue Specific Gene Therapy to Neovascular Tumoral-Endothelial Cells".

1997-2000      Pnina Keren          Ph.D.  
**Thesis:**       "Diabetes in Transgenic Mouse Model of Atherosclerosis".  
*Graduate Cum Laude*

1997-1999      Einat Golan          M.Sc.  
**Thesis:**       "Regulation of LDL-Receptor Expression in Lovastatin Resistant Cells".

1998-            Yariv Gerber        Ph.D.  
**Thesis:**       "Apo CII, CIII, TG & Atherosclerotic Cardiovascular Diseases"

1998-            Ayelet Gonon        M.Sc.  
**Thesis:**       "Adenoviral Gene Therapy to Neovascular Tumoral-Endothelial Cells"

1998-            Grinberger Shoshi MD    Ph.D.  
**Thesis:**       "Induction of Apoptosis in Endothelial Cells"

**G.2 M.Sc. & Ph.D. STUDENTS (cont.)**

- 1999- Keren Levanon MD/Ph.D.  
**Thesis:** "Adenoviral Gene Therapy for Induction of Angiogenesis and vessel maturation."
- 2001- Ayelet Gonen Ph.D.  
**Thesis:** "The effect of Allicin derivatives on atherosclerosis mode of actions."
- 2001- Israel Hodish MD Ph.D.  
**Thesis:** "Engineering of adeno-viral vector containing the HSV-TK gene under the control of murine pre-proendothelin promoter for the treatment of cancer".

**G.3 Resident's basic science projects supervised by candidate**

- 1999 Arnon Afek Basic-science  
**Thesis:** "Anti-HSP65-antibodies and atherosclerosis in LDL-Receptor deficient mice".
- 1998 Rafael Bitzur Basic science  
**Thesis:** "Induction of IDDM in Transgenic Mouse Model of Atherosclerosis".
- 1997 Jakob George Basic-science  
**Thesis:** "Anti-phospholipids-antibodies and atherosclerosis in LDL-Receptor deficient mice".
- 1997 Peer Dar Zitser Basic-science  
**Thesis:** "15 Lipoxygenase overexpression reduces fertility in Tg mice".
- 1999 Swetlana Poyerovski Basic-science  
**Thesis:** "הקר הגנטיקה של COPD בשושלת יוּהסִין מבודדת בישראל."
- 1999 Eyal Leibovitz Basic-science  
**Thesis:** "The Association between the polymorphism of the human Paraoxonase gene with plasma Paraoxonase activity and coronary artery disease in Israeli Jewish population."

**G.3 Resident's basic science projects supervised by candidate (cont.)**

- 1999            Lea Hananashvili      Basic-science  
Thesis: "Efficacy of the combination of Fibrates and 9 cis Retinoic Acid on the lipid profile of human Apo A1 transgenic mice".
- 2000            Roy Ilan                 Basic-science  
Thesis: "Amplification of gene expression in transfected cardiomyocytes by ultrasound."
- 2000            Levi Zohar              Basic-science  
Thesis: "The effect of the natural isomer mixture of β-carotene from the alga Dunaliella on the degree and extent of atherosclerosis in apo E deficient mice."
- 2000-2001      Swetlana Trastman    Basic-science  
Thesis: "The effect of the cytokine interferon-α on the degree of atherosclerosis in LDL receptor deficient mice".
- 2001            Afek Limor              Basic-science  
Thesis: "Oral Tolerance to ox-LDL in LDL-Receptor deficient mice."
- 2001            Vladimir Chesnin      Basic-science  
Thesis: "Plasma levels and distribution of CII and CIII apolipoproteins: Are they risk factors for Alzheimer's disease?"
- 1999-2000      Hagith Yonath          Basic-science  
Thesis: "Inter-individual variability in sensitivity to warfarin – nature or nurture?"
- 2001            Marunich Anastasya    Basic-science  
Thesis: "The effect of the natural isomer mixture of β-carotene from the alga Dunaliella on the degree and extent of atherosclerosis in apo E deficient mice."

## TEACHING EXPERIENCE

### **Hebrew University Hadassah Medical School, 1988-1991.**

Teaching activities before my departure to the USA.

- 1990 Coordinator of a course in internal medicine for 6th year medical students.
- 1990-1989 Coordinator of the course in cardiopulmonary resuscitation for 6th year medical students.
- 1988-1991 Coordinator of the course in internal medicine for Biotechnicians at the Hadassah College.
- 1989 Award for Outstanding lecturer at the Hebrew University Hadassah Medical School.
- 1988-1991 Teaching internal medicine to 4th year medical students.
- 1990-1991 Supervising an M.D. thesis work at the Hebrew University Hadassah Medical School. "Lipid peroxides in down's syndrome: A study related to the paucity of atherosclerosis in this condition."
- 1990-1991 Member in the Hebrew University Hadassah Medical School Committee, interviewing candidates for medical school.
- 1990-1991 Teaching in the course of medicine to the new emigrants MDs from the USSR, at the Hebrew University Hadassah Medical School.
- 1991 Preparing the Boards in Internal Medicine for Medical Graduate at the Hebrew University Hadassah Medical School.

### **Sackler Faculty of Medicine, Tel Aviv University, 1995.**

I returned to Israel from the USA in December 1994, since than I am involve in the following teaching activities.

- 1998- 2002 Member of the Medical School Teaching Committee ( ועדת הוראה )
- 1998- 2001 Organizing the "Basic Science Correlate Course".
- 1998- 2000 Member of the Committee for Organizing the Clinical Studies Curriculum
- 1998- 2000 Member of the Committee for Organizing the Basic Studies Curriculum
- 1998- 1999 Head of the subcommittee for teaching facilities in the clinical years.
- 1997- 2002 Teaching in the PostGraduate School of Medicine; "Lipids and Lipoprotein Metabolism."
- 1995- 2002 Teaching in the course of Biochemistry for first and third year medical students; "Lipids and Lipoprotein Metabolism."
- 1995- 2002 Teaching fourth year medical students in the course of Internal Medicine; "Hyperlipidemia & Atherosclerosis."
- 1995- 2002 Teaching fourth year medical students (both the NY and the regular program) in the courses Pulmonary medicine.
- 1995- 2002 Teaching in the "Gene Therapy" course for M.Sc. & Ph.D. students.
- 1995- 2002 Seminars in gene therapy to physicians and researchers at Tel Hashomer.

**LIST OF PUBLICATIONS****A. Book Written**

1. Shoenfeld, Y., Harats, D., Wick, G.  
Atherosclerosis and Autoimmunity.  
Elsevier, 370pp, 2001.

**B.1. Original Article****1. Published**

1. Stein, Y., Halperin, G., Harats, D., Stein, O.  
Metabolic fate and effect on cholesterol removal of liposomes prepared from 1,3-di-o-octadecenylglycero-2-phosphocholine studied in vivo and in vitro.  
Biochim. Biophys. Acta 922: 191-198, 1987.
2. Harats, D., Stein, O., Schwartz, R., Berry, E. M., Stein, Y.  
Preferential metabolism by macrophages of conditioned rabbit hypercholesterolemic remnant lipoproteins.  
Biochim. Biophys. Acta 959: 127-133, 1988.
3. Stein, O., Oette, K., Harats, D., Halperin, G., Stein, Y.  
Sphingomyelin liposomes with defined fatty acids: metabolism and effects on reverse cholesterol transport.  
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Quart. J. Med. 92(1):57-59,1999.

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13. Yehuda Shoenfeld, Yaniv Sherer, Yaakov George, Dror Harats.  
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Ceramide pathway and apoptosis in autoimmunity and atherosclerosis.  
In: Atherosclerosis and Autoimmunity; Elsevier, 73-86, 2001.
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Diabetes Mellitus in the 3<sup>rd</sup> millennium, 117-130, 2001  
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**D.1. Invited papers in scientific meeting**

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Lipoproteins, smooth muscle cells and macrophages.

In: Proceedings of 8th intl. Symposium Atherosclerosis, Rome, Atherosclerosis VIII, ed. G. Crepaldi, Excerpta Medica: 81-84, 1988.

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Metabolic fate and effect on cholesterol removal of liposomes prepared from 1,3-di-octadecenylglycero-2-phosphocholine studied in vivo and in vitro.

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In the proceedings of the 64th European Atherosclerosis Society, Utrecht, Netherlands, S41, 1995.

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15-Lipoxygenase overexpression induces atherosclerosis in LDL -receptor deficient mice.

Circulation (134) 279, 1997.

5. Harats, D.

The immune system in atherogenesis.

In the proceedings of the 4<sup>th</sup> Annual Meeting of the Society for Research, Prevention and Treatment of Atherosclerosis, Eilat, Israel, 1998.

6. Harats, D., George, J., Afek, A., Gillburd, B., Levkovitz, H., Shaish, A., Kopolovitz, Y., Wick, G., Shoenfeld, Y.

Immunomodulation of atherogenesis.

In the proceedings of the 70<sup>th</sup> EAS, Geneva, Switzerland, 1998.

7. Harats, D., George, J., Gillburd, B., Afek, A., Shaish, A., Shoenfeld, Y.

Beta 2 glycoprotein I (Apolipoprotein-H) as an influential determinant in atherosclerosis.

In the proceedings of the 71<sup>st</sup> ESA congress, Athens, Greece, May 1999.

8. D. Harats, J. George, B. Gilburd, A. Afek, A. Shaish, Y. Shaish.

Adoptive transfer of  $\beta$ 2-glycoprotein I reactive lymphocyte enhances atherosclerosis in LDL receptor deficient mice In the proceedings of the 12<sup>th</sup> ISA, Stockholm, Sweden, 2000.

9. D. Harats.

The Immune system in Atherosclerosis. In the proceedings of the 37<sup>th</sup> EASD, Glasgow, Scotland, 2001.

**D.2. Papers presented at scientific meetings**

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2. Stein, Y., Berry, E. M., Eisenberg, S., Harats, D., Friedlander, Y., Norman, Y., Kaufmann, N.

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Fish oil ingestion in smokers and nonsmokers enhances peroxidation of plasma lipoproteins; attenuating effect of vitamin E

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Using transgenic mice to investigate *in vivo* biology of lipoxygenases.  
The 9th International Conference on Prostaglandins & Related Compounds, Florence, June, 1994.

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Hyperimmunization of chow fed apo-E defficient mice with homologous oxidized Low Density Lipoprotein suppresses early atherogenesis.

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15-Lipoxygenase overexpression induces atherosclerosis in LDL -receptor deficient mice.

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“Enhanced fatty streak formation in C57BL/6 mice by immunization with heat-shock protein 65”

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The Role of Heat Shock Protein 65 (HSP) in Murine Atherosclerosis.

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**D.3. Abstracts and Proceedings. (cont.)**

**16. Harats, D., Kurihara, H., Levkovitz., Sigal, E.**

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**D.3. Abstracts and Proceedings. (cont.)**

31. George, J., Shoenfeld, Y., Afek, A., Gillburd, B., Keren, P., Shaish, A., Kopolovitz, Y., Wick, G., and Harats, D.

"Enhanced fatty streak formation in C57BL/6 mice by immunization with heat-shock protein 65"

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## Oral

### Administration



Antigen

Tolerance

Feeding

Immunity

(*hypo-responsiveness*) GALT (*hyper-responsiveness*)

↓  
T-Cell Proliferation

to Antigen

↑  
T-Cell Proliferation

to Antigen

/Clonal Deletion)  
Immune Modulation  
Immune Response

(Clonal Anergy

Th<sub>1</sub> → Th<sub>2</sub>

IL-10 ↑

IFN-γ ↓

Th<sub>1</sub>  
IL-10 ↓  
IFN-γ ↑

Antibody formation

## PANEL II

